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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/066,390	02/01/2002	Hal S. Padgett	P-LG 4878	4639

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EXAMINER	
STRZELECKA, TERESA E	

ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/066,390	PADGETT ET AL.	
	Examiner	Art Unit	
	TERESA E. STRZELECKA	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *91-105* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *91-105* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/21/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This office action is in response to an amendment filed May 21, 2008. Claims 66-72, 78-83, 85 and 87-105 were previously pending. Applicants cancelled claims 66-72, 78-83, 85 and 87-90 and amended claims 91 and 104. Claims 91-105 are pending and will be examined.

2. Applicants' claim cancellations overcame all of the previously presented rejections for claims 66-72, 78-83, 85 and 87-90.

3. The declaration of Dr. Hal Padgett under 37 CFR 1.132 filed May 21, 2008 is sufficient to overcome the rejection of claims 91-105 based upon the combination of references of Arnold et al. and Oleykowski et al.

4. Applicants did not submit terminal disclaimers, therefore the obviousness-type double patenting rejections of claims 91-98, 100, 102-104 are maintained.

5. This office action is made non-final because of new grounds for rejection for claims 91-105.

Information Disclosure Statement

6. The information disclosure statement (IDS) submitted on May 21, 2008 was filed after the mailing date of the non-final office action on February 21, 2008. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 91 and 93-105 are rejected under 35 U.S.C. 103(a) as being unpatentable over Arnold et al. (WO 99/29902; cited in the IDS and in the previous office action), as evidenced by Lahue et al. (Science, vol. 245, pp. 160-164, 1989; cited in the previous office action), Birkenkamp et al (DNA Research (1995) 2:9-14; cited in the previous office action), Youil et al. (PNAS USA, vol. 92, pp. 87-91, 1995; cited in the previous office action) and Oleykowski et al. (Nucl. Acids Res., vol. 26, pp. 4597-4602, 1998; cited in the previous office action).

A) Regarding claim 91, Arnold et al teach an in vitro method of making linear sequence variants comprising:

a) preparing at least one heteroduplex polynucleotide, the heteroduplex having first and second strands (page 2, lines 32, 33; page 3, lines 1-5; lines 11-33; page 4, lines 1-9; since heteroduplex is a double-stranded nucleic acid, it inherently has first and second strands),

b) combining said heteroduplex polynucleotide with enzymes comprising an effective amount of a mismatch directed endonuclease, an enzyme or enzymes with 3' to 5' exonuclease activity and an enzyme or enzymes with polymerase activity (Arnold et al. teach mixing the heteroduplexes with either intact cells or cell extracts containing mismatch-endonuclease activity, an enzyme with 3' to 5' exonuclease activity and enzyme with polymerase activity (page 3, lines 2-5;10; page 4, lines 24-26; page 9, lines 12-33; page 16, lines 22-33; page 17, lines 1-33; page 18, lines 1-3). As evidenced by Lahue et al., E. coli contains a DNA polymerase and a ligase which participate in the repair reactions (page 161, second paragraph), therefore by teaching E. coli cells Arnold et al. inherently teach a polymerase. Further, since the E. coli cells contain a repair system which contains cellular repair system with mismatch endonuclease, Arnold et al. inherently teach mismatch endonuclease. Finally, E. coli cells contain enzymes with 3' to 5' exonuclease activity, for example DNA polymerase PolI.),

c) allowing sufficient time for the percentage of complementarity to increase wherein one or more sequence variants are made, thereby increasing diversity in a population of polynucleotides (Arnold et al. teach allowing sufficient time to proceed with a repair mechanism and produce variant nucleotides (page 18, lines 6-8), therefore inherently increasing diversity of a population of polynucleotides and producing at least one variant), and

d) separating and recovering at least one sequence variant having a sequence different from either polynucleotide strand in said heteroduplex (page 3, lines 11-25), where resulting nucleic acids are inherently separated and recovered by cloning).

Regarding claim 93, Arnold et al. teach concurrent addition of the exonuclease, polymerase and strand cleavage enzymes (page 9, lines 21-22, where the cell extract is added).

Regarding claims 94-96, Arnold et al. teach the addition of E. coli DNA ligase in cell extracts (page 9, lines 21-22; page 17, line 33; where the cell extract from E. coli is added, which inherently includes E. coli ligase).

Regarding claims 98 and 99, Arnold et al. teach the addition of E. coli DNA polymerase I in cell extracts (page 9, lines 21-22, page 17, line 33; where the cell extract from E. coli is added which inherently includes E. coli DNA polymerase I).

Regarding claim 101, Arnold et al. teach that the complementarity increases, resulting in homoduplex polynucleotides and an increase in diversity of the population (page 23, lines 10-32; page 24, lines 1-8).

Regarding claim 102, Arnold et al. teach performance of the method to generate a library of different nucleotide sequences (page 23, lines 10-32; page 24, lines 1-8, for example).

Regarding claims 103and 104, Arnold et al. teach screening for changed properties of the sequence (page 3, lines 4, 5; page 4, lines 27-30; page 6, lines 30-33; page 7, lines 1-5; page 9, lines 30-33; page 18, lines 30; page 19, lines 1-9).

Regarding claim 105, Arnold et al. teach 56% homology can be used which would result in at least three non-complementary base pairs that performance of the method will generate at least four sequence variants (page 22, 23, page 24, lines 1-8, for example).

B) Arnold et al. do not teach plant mismatch-directed endonuclease or using a mismatch-correction system comprising isolated polypeptides with mismatch endonuclease, exonuclease, ligase and polymerase functions.

Arnold et al. expressly teach that a variety of different mismatch repair systems can be used (page 16, lines 22-32; page 17, lines 1-23).

C) Regarding claims 91 and 96-98, Birkenkamp et al. teach an in vitro method (see figure 2) of making linear sequence variants (see figure 1, where hairpins are linear), using the T4 mismatch correction system, including T4 endonuclease VII, T4 DNA ligase and T4 DNA polymerase (see page 11, column 1). They also teach that T4 endonuclease is used for mapping mutations in heteroduplexes by Youil et al. (page 13, third paragraph).

Youil et al. teach using T4 endonuclease VII to detect mutations in DNA heteroduplexes (Abstract; page 87, second paragraph; page 88, last paragraph; page 89; Fig. 2-4).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the T4 mismatch correction system as an alternative to the E. coli cell extract in the in vitro mismatch repair method of Arnold et al. since Birkenkamp et al. teach:

"In summary, these observations emphasize further the in vivo role of endonuclease VII as a repair-initiating enzyme that recognizes a wide variety of DNA secondary structures (see page 13, column 2)".

The motivation to do so, provided by Youil et al., would have been, as stated by Youil et al. (page 87, first paragraph):

"The detection of mutations is important, particularly in the diagnosis of inherited diseases. Changes in the DNA sequences of a gene can be harmful and it is important in our understanding of human genetics that we are able to identify and classify these alterations and the phenotypic changes that they induce. Consequently, the need for a reliable method for the detection of mutations in DNA to avoid repetitive sequencing of kilobase lengths of DNA has led to the development of a number of different screening methods that have both positive and negative attributes (see ref. 1 for a review of current mutation detection methods)."

Finally, since Birkenkamp et al. teach that the T4 system is a known equivalent in the prior art of the other systems detailed by Arnold et al., this falls within the situation described in MPEP 2144.06, which notes "Substituting equivalents known for the same purpose. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout , 675 F.2d 297, 213 USPQ 532 (CCPA 1982)."

D) Neither Arnold et al. nor Birkenkamp et al. teach plant endonuclease or Cel I endonuclease.

E) Regarding claims 91 and 100, Oleykowski et al. teach that Cel I endonuclease, derived from celery, is a superior enzyme for mismatch correction (see page 4602, column 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the Cel I endonuclease of Oleykowski et al. in the in vitro mismatch repair method of Arnold et al., Birkenkamp et al. and Youil et al., since Oleykowski et al. state,

"The principle of mismatch recognition by CEL I appears to be different from T4 endonuclease VII, which has also been used for enzyme mutation detection. The latter is a resolvase which nicks one strand at the site of a mismatch and then in the other strand across from the DNA nick. Therefore, any nick can produce two corresponding fragments of the two colors. In the case of CEL 1, the two fragments of the two colors represent two totally independent mutation detection events that complement each other to confirm the presence of the mutation. (See page 4602, column 1)."

Oleykowski et al. further note "Other strengths of the CEL I mutation detection assay are its simplicity and its lack of preference for unique non-mismatch DNA sequences. Background non-specific DNA nicking is very low. The high signal-to-noise ratio of CEL I using fluorescent dye-labeled PCR products often allows mutations to be detected by visual inspection of the GeneScan gel image. CEL I is a very stable enzyme, during both its purification, storage and assay (see page 4602, columns 1 and 2)."

So, an ordinary practitioner would have two separate motivations to use CEL 1 in the method of Arnold et al., Birkenkamp et al. and Youil et al. in the place of the other mismatch correction systems. First, CEL 1 operates differently than T4 endonuclease VII and only nicks one strand to result in truly independent mutation event detection. Second, CEL I mutation detection is

simple, with low background nicking, high signal to noise ratio and uses a stable enzyme, which minimizes wasted effort in assays where the enzyme fails to function.

9. Claim 92 is rejected under 35 U.S.C. 103(a) as being unpatentable over Arnold et al. (WO 99/29902; cited in the IDS and in the previous office action), as evidenced by Lahue et al. (Science, vol. 245, pp. 160-164, 1989; cited in the previous office action), Birkenkamp et al (DNA Research (1995) 2:9-14; cited in the previous office action), Youil et al. (PNAS USA, vol. 92, pp. 87-91, 1995; cited in the previous office action) and Oleykowski et al. (Nucl. Acids Res., vol. 26, pp. 4597-4602, 1998; cited in the previous office action).

A) Arnold et al. teach addition of all of the ingredients at once, but do not teach adding the ingredients in the particular order claimed in claim 92.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use any order of adding ingredients, as MPEP 2144.04 IV.C notes "Selection of any order of mixing ingredients is prima facie obvious." Here, there is no particular reason why the order is shown to have any effect on the reaction other than to add the first necessary reactant first, the second and the third reactant needed is added last. So in the absence of any evidence of unexpected results with regard to the order of addition, the claimed order is prima facie obvious as noted by the MPEP section above.

Double Patenting

10. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re*

Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claims 91-98, 100 and 102-104 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 4 and 6 of U.S. Patent No. 7,217,514. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1, 4 and 6 of the '514 patent are species of claims 91-98, 100 and 102-104 of the instant application.

Specifically, claim 1 of the '514 patent is drawn to an in vitro method of making circular sequence variants from one or more circular heteroduplex polynucleotides wherein said heteroduplex polynucleotides have at least two non-complementary nucleotide base pairs separated by complementary nucleotide base pairs, said method comprising:

a) preparing the one or more circular heteroduplex polynucleotides;

b) sequentially or concurrently combining said circular heteroduplex polynueleotides with purified enzymes wherein the enzymes consist essentially of an effective amount of a mismatch recognizing and mismatch directed endonuclease CEL I, T4 DNA polymerase, and E. coli DNA ligase;

c) allowing sufficient time for the percentage of complementarity and diversity in a population of polynucleotides to increase such that one or more circular sequence variants are made which are different from the circular heteroduplex polynueleotides, and which contain a partial sequence matching each polynucleotide in the circular heteroduplex polynueleotides;

d) separating said sequence variants from the polynucleotides which make up the circular heteroduplex polynucleotide; and

e) recovering said circular sequence variants, wherein at least one circular sequence variant has a different desired functional property from the polynucleotides in said one or more circular heteroduplex polynucleotides.

Therefore, claim 1 of the '514 patent anticipates claims 91-98, 100 and 104 of the instant application. Claims 4 and 6 of the '514 patent anticipate instant claims 102 and 103.

12. Claims 91, 94, 100 and 102-104 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 6 of U.S. Patent No. 7,235,386. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1 and 6 of the '386 patent are species of claims 91, 94, 100 and 102-104 of the instant application.

Specifically, claim 1 of the '386 patent is drawn to a method of obtaining a polynucleotide variant comprising the steps of:

a) preparing at least one first heteroduplex polynucleotide from partially complementary polynucleotide strands, said first heteroduplex polynucleotide having at least two mismatched base pairs;

b) combining said heteroduplex polynucleotide with an effective amount of purified enzymes, wherein the enzymes comprise a polymerase, a ligase and a mismatch directed endonuclease selected from the group consisting of CEL I, T4 endonuclease VII, T7 endonuclease I, and SP nuclease;

c) allowing sufficient time for the percentage of complementarity between the strands of said heteroduplex polynucleotide to increase so that variants are made that have sequences different from any of said partially complementary polynucleotide strands;

d) screening or selecting for a population of variants having a desired functional property from the variants; denaturing at least one of said population of variants to obtain single strand polynucleotides;

f) annealing said single strand polynucleotides to form at least one second heteroduplex polynucleotide, wherein at least one strand in the second heteroduplex is a variant and said second heteroduplex polynucleotide has at least two mismatched base pairs;

g) combining said second heteroduplex polynucleotide with an effective amount of purified enzymes, wherein the enzymes comprise a polymerase, a ligase, and a mismatch directed endonuclease selected from the group consisting of CEL I, T4 endonuclease VII, T7 endonuclease I, and SP nuclease;

h) allowing sufficient time for the percentage of complementarity between the strands of the heteroduplex polynucleotide to increase so that additional variants are made that have sequences different from any of the partially complementary polynucleotide strands and different from any of the variants made in step c), and being different from either strand in the second heteroduplex;

i) screening or selecting for a population of additional variants having a desired functional property from the additional variants different from any of the variants made in step c) and different from any of said partially complementary polynucleotide strands; and

j) recovering an additional variant from the population of additional variants.

Therefore, claim 1 of the '386 patent anticipates claims 91, 94, 100, 102 and 103 of the instant application. Further, claim 6 of the '386 patent anticipates claim 104.

13. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TERESA E. STRZELECKA whose telephone number is (571)272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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